ORIGINAL ARTICLE

The feasibility of antibiotic dosing four times per day: A prospective observational study in primary health care

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Abstract

Objective. To investigate whether the increase in the number of doses of penicillin V from three times daily to four times daily for common infections, as recommended in the new Norwegian guidelines for antibiotic treatment in primary health care, would lead to reduced patient compliance. **Design.** Prospective observational study. **Setting and subjects.** Six general practitioners included all patients who were prescribed systemic antibiotic treatment regardless of indication during a 10-month period. A total of 270 patients provided data for the study. **Methods.** Telephone interview focusing on omitted antibiotic doses. **Results.** Some 17% of patients had poor compliance, defined as failing to take 5% or more of total antibiotic doses. Neither level of poor compliance nor number of omitted doses differed significantly when the number of daily doses increased from three to four. There were significantly fewer omitted doses in the group given two doses per day when compared with three doses ($p = 0.04$) and four doses per day ($p = 0.01$). **Conclusion.** We found no difference in compliance or omitted doses between antibiotic regimens of three and four doses per day. The new Norwegian guidelines for antibiotic treatment in primary health care appear feasible with regard to patient compliance.

Key Words: Antibiotics, guidelines, Norway, patient non-compliance, primary care, treatment

Introduction

In 2008, the Antibiotic Center for Primary Health Care at the University of Oslo published new national guidelines for antibiotic treatment in primary health care [1,2]. A significant alteration from earlier practice was the recommended increase in dose frequency for penicillin V from three to four doses per day for common infections such as pneumonia and erysipelas. We suspected that this increase could lead to reduced patient compliance.

Non-compliance is defined as any deviation by a patient from a doctor's instruction and is a common problem in long-term treatment for chronic diseases [3,4]. Non-compliance is also seen with short-term antibiotic treatment [5]. Studies have shown that compliance decreases with increasing number of doses per day and when treatment duration is seven days or more [6]. We were not able to identify any studies addressing compliance in short-term antibiotic treatment in a Scandinavian setting.

Norway has a low rate of antibiotic usage, and is one of the countries in Europe with the lowest occurrence of bacterial resistance to antibiotics [7,8]. Penicillin V is recommended as first-line treatment for nearly all bacterial airway infections and for many soft-tissue infections [1].

Traditionally, penicillin V has been given thrice daily with a double dose at night. This practice is not logical when taking into consideration recent pharmacokinetic and pharmacodynamic insights [9]. Penicillin V has a short half-life (30–60 min) and a short post-antibiotic effect. Regrowth of most organisms will commence soon after serum level of penicillin decreases below the minimal inhibitory concentration (MIC) [9]. As for most other antibiotics commonly used in general practice, both a clinical and microbiological effect of penicillin V can be assumed if serum levels are above MIC for more than 50% of the period between two doses [9,10]. This means that the optimal theoretical dosage is at least

Compliance with antibiotic treatment has been shown to decrease with increasing dose frequency. New Norwegian guidelines for antibiotic treatment in primary health care recommend penicillin V dosing four times per day as compared with three times per day in earlier recommendations.

- An overall good compliance with treatment was found, even with regimens of four doses per day.
- There was no significant difference in compliance when comparing four antibiotic doses per day with three doses per day.
- The new Norwegian guidelines for antibiotic treatment in primary health care appear feasible in clinical practice.

four times a day. The effect of giving a double dose at night is small, prolonging the time when the penicillin serum concentration is above the minimum inhibitory concentration (MIC) by one half-life, approximately 30 min. No studies were identified that investigated the clinical relevance of dosing frequency during treatment with penicillin V in primary health care in terms of resistance development or clinical effectiveness.

The aim of this study was to investigate whether the recommendations in the National Guidelines for antibiotic treatment in primary health care with regard to the increased dose frequency of penicillin V were feasible in clinical practice [1]. Our hypothesis was that compliance would decrease as the number of daily doses increased from three to four.

Material and methods

We performed a prospective observational study in a primary care setting. Over a period of 10 months in 2010, six general practitioners (GPs) at two different group practices in southern Norway included patients. All patients who received a prescription for systemic antibiotics were included, regardless of indication. Exclusion criteria were antibiotics given in a liquid form and patients who had their medication administered by the home nursing service. The patients gave written consent to be contacted by the authors after the treatment period. No details were given regarding the aim of the study. The prescribing doctor registered the indication for treatment, which antibiotic was given, length of treatment, number of doses per day, and the number of tablets prescribed. The authors (TBE and VCH) contacted all patients by phone within a week after the last day of treat-

Table I. Questions asked: Compliance with antibiotic treatment among 270 patients in Norwegian general practice.

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- In your opinion, were you seriously ill before starting the treatment?
 - Did you take the medication according to the doctor's recommendation?
 - Did you fail to take any of the doses?
 - Do you have remaining tablets? If yes, how many?
 - Did you stop the treatment before you were meant to? If yes, why?
 - Do you feel well now?
 - Did you get any adverse effects from the medication?
 - Did you get the treatment from your regular doctor?
-

ment. They were asked a standardized set of questions (Table I).

A total of 296 patients were included. No patients rejected participation. Of the included patients, 13 were lost to follow up, and were subsequently excluded from the analysis; a further 13 patients had to change drug due to adverse effects or were admitted to hospital and were also excluded. Thus, 270 patients provided data for this study.

We defined poor compliance as failing to take 5% or more of the total number of antibiotic doses during the course. Patients who ceased treatment too early without consulting a doctor were defined as having failed to take all doses for the remaining days. Patients who failed to take some doses but continued the treatment until they had no remaining tablets were still defined as having failed to take the doses.

Statistics and ethics

Statistical analyses were carried out by means of the program PASW Statistics 18 (SPSS Inc., Chicago, Ill.). Differences in omitted doses between groups were compared using an independent samples t-test, whereas between-groups levels of poor compliance were investigated by means of Fisher's exact test.

The study was accepted by the Regional Committee for Medical and Health Research Ethics. It has been registered in the database Clinical Trials.gov Protocol Registration System (NCT01291251).

Results

A total of 196 women (72.6%) and 74 men (27.4%) were included in the analysis. Age varied from four to 92 years, with a mean of 43.5 years. The indications for treatment are presented in Table II, and the antibiotics used are listed in Table III. One hundred and fifty-nine patients (58.9%) received the prescription from their regular GP, whereas 109 (40.4%) had seen another doctor in the same group practice. In

Table II. Indications for treatment: Compliance with antibiotic treatment among 270 patients in Norwegian general practice.

	n (270)	%
Lower airway infection	115	42.6
Sinusitis	44	16.3
Urinary tract infection	38	14.1
Tonsillitis	37	13.7
Soft-tissue infection	26	9.6
Otitis	7	2.6
Others ¹	3	1.1

Note: ¹Others: Pelvic inflammatory disease and diverticulitis.

two cases, the doctor could not be identified. The antibiotic courses lasted from three to 14 days. The number of doses per day varied from one to four (Table IV).

No patients receiving once-daily dosing reported having omitted any doses. There was no significant difference in the actual number of omitted doses when comparing patients receiving three doses a day with patients receiving four doses ($p = 0.4$, independent samples t-test), whereas patients receiving two doses a day omitted significantly fewer doses compared with patients taking three ($p = 0.04$) or four ($p = 0.01$) doses a day (see Table IV).

A total of 46 patients (17%) had poor compliance when defined as omitting 5% or more of all doses. There was no significant difference in poor compliance when the groups taking three or four doses a day were compared (see Table IV). If the patients given one or two doses per day were grouped and compared with patients given three or four doses per day, there was still no significant difference in compliance. Furthermore, there was no significant difference when patients given four doses a day were compared with all other groups. We saw no difference in compliance related to the patient's gender, whether the patient felt

Table III. Prescribed antibiotics: Compliance with antibiotic treatment among 270 patients in Norwegian general practice.

Drug	n (270)	%
Phenoxymethylpenicillin	105	38.9
Erythromycin	54	20.0
Doxycycline	21	7.8
Dicloxacillin	18	6.7
Mecillinam	18	6.7
Trimethoprim	16	5.9
Amoxicillin	12	4.4
Clarithromycin	11	4.1
Azithromycin	6	2.2
Ciprofloxacin	2	0.7
Others ¹	7	2.6

Note: ¹Others: Metronidazole, trimethoprim-sulfamethoxazole, cefalexin, clindamycin, nitrofurantoin.

Table IV. Compliance related to number of doses per day: Compliance with antibiotic treatment among 270 patients in Norwegian general practice.

Doses per day	Number of patients (%)	Number of omitted doses: mean 95% CI (min.-max.)	Number of poor compliers ¹ n (%)
1	17 (6.3)	0 – (0–0)	0 (0)
2	61 (22.6)	0.3* 0.14, 0.45 (0–2)	13 (21.3)
3	107 (39.6)	0.71 0.34, 1.08 (0–12)	15 (14.0)
4	85 (31.5)	0.95 0.46, 1.47 (0–14)	18 (21.2)
1 or 2	78 (28.9)	0.23 – (0–2)**	13 (16.7)
3 or 4	192 (71.1)	0.82 – (0–14)	33 (17.1)

Notes: ¹Defined as failing to take 5% or more of all doses. No significant differences between groups (Fisher's exact test). * $p = 0.04$ for two doses versus three doses and $p = 0.01$ for two doses versus four doses (independent samples t-test). ** $p < 0.01$ versus three or four doses (independent samples t-test).

seriously ill or not, whether the medication was prescribed by the patient's regular doctor or not, or the length of the treatment (data not shown in Table).

Discussion

The main aim of this study was to investigate whether the recommended increase from three to four daily doses of penicillin V would lead to reduced compliance [1]. We found no significant difference in either the level of compliance or in the number of missed doses when the number of daily doses increased from three to four.

The relatively small number of patients taking one daily dose ($n = 17$) reported a 100% compliance, and patients taking two doses a day missed fewer doses than patients taking three or four doses. The significance of a specific number of omitted doses will, however, vary according to the total number of doses in the course and the pharmacodynamic and -kinetic properties of the drug given. The rate of poor compliance defined as omitting $\geq 5\%$ of total doses did not show a significant variation between the groups. This study showed an overall high compliance, even with regimens of four doses per day, where four out of five patients reported taking 95% or more of the prescribed doses.

The optimal method of tracing reduced compliance would be to randomize patients to three or four doses. This study is a pragmatic, observational study, investigating “business as usual” in general practice. No calculation of number of patients needed to secure statistical power was performed. The possibility exists that by expanding the study we would find a significant fall in compliance, a possibility supported by the relatively wide 95% CI for omitted doses shown in Table IV.

Similar studies conducted in other countries have demonstrated poor compliance with antibiotic treatment regimens exceeding one dose per day [5,6,11]. Llor et al. found that 55.1% of the patients in the thrice-daily group took at least 80% of the medication, whereas the corresponding numbers in the twice- and once-daily group were 71.4% and 86.7% respectively [5]. It has been concluded that GPs should aim at choosing medication that can be given once or twice daily [5,6].

Other studies have defined good compliance as taking at least 80% of the prescribed doses [12]. This implies that in a 10-day course with four doses per day the patient can fail to take up to eight doses and still be registered as a compliant patient. In our material, only seven persons of a total of 270 (2.6%) would thus be registered as poorly compliant. Our study design dictated that we chose a strict definition of poor compliance as failing to take 5% or more of the total number of doses.

Information regarding both dose taking (taking the prescribed number of tablets each day) and dose timing (taking the tablets within a prescribed period) are of importance when evaluating compliance [12]. Earlier studies have reported that compliance regarding drug taking was better than timing compliance [5]. The best indirect method to measure compliance with medication is the Medication-Event Monitoring System (MEMS), which registers electronically how many times and at which hours the tablet box has been opened [6]. Our study relied on the patient's report only. Some patients may have reported a falsely high compliance.

Compliance has been shown to increase with the use of laboratory tests [13], and is also related to the quality, duration, and frequency of interaction between the patient and the doctor [14]. In our study, all patients had their medication prescribed either from their regular doctor or from a doctor in the same group practice. This may increase the trust in the treatment given, and increase the patient's loyalty to the treatment prescribed. In Norway, there is traditionally a restrictive practice regarding the prescription of antibiotics [7]. Many patients are likely to be aware of this, which may lead to the attitude that doctors only give antibiotics when it is essential. This may in turn increase compliance.

The results of a similar study might therefore have been different in another health care system.

In Norway, 84% of all antibiotics are prescribed in the primary health care system [8]. The Norwegian guidelines for antibiotic treatment in primary health care recommend drugs that are likely to cure the infection in question, but also aim to encourage GPs to choose antibiotics with a narrow spectrum to minimize the risk of antibiotic resistance. If patients are not able to comply with a regimen of four times daily dosing, this will, for penicillin V, result in more time below the MIC and increase the probability of resistance development.

The main goal with this study was to clarify whether a penicillin V regimen of four doses per day would result in a significantly lower compliance when compared with three doses per day. In similar studies in other countries, the main outcome has been a decrease in compliance with increasing dose frequency, and the recommendation has therefore been that doctors should choose once- or twice-daily treatment regimens [5,6]. Antibiotics available for regimens of one or two doses per day are mainly broad-spectrum drugs. If GPs choose broad-spectrum antibiotics because they presume that patients cannot manage a treatment regimen of three or four doses a day, this may lead to an unfortunate increase in bacterial resistance. This study does not support such an action, as patients seem to comply with three and even four doses per day. We conclude that the new guidelines for dosing of penicillin V are feasible in clinical practice.

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Declaration of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

References

- [1] Lindbak M, editor (Antibiotic Centre for Primary Care, University of Oslo, Norway). Nasjonale faglige retningslinjer for antibiotikabruk i primærhelsetjenesten [National guidelines for the use of antibiotics in primary health care]. Oslo, Nor-

- way: Norwegian Directorate of Health; 2008. ISBN 978-82-8081-112-7.
- [2] Eliassen KE, Fetveit A, Hjortdahl P, Berild D, Lindbæk M. Nye retningslinjer for antibiotikabruk i primærhelsetjenesten [New guidelines for antibiotic use in primary health care]. *Tidsskr Nor Laegeforen* 2008;128:2330-4 (English summary).
 - [3] Lardizabal J, Deedwania P. Benefits of statin therapy and compliance in high risk cardiovascular patients. *Vasc Health Risk Manag* 2010;6:843-53.
 - [4] Faught E, Weiner JR, Guerin A, Cunnington MC. Nonadherence to antiepileptic drugs and increased mortality. *Neurology* 2008;71:1572-8.
 - [5] Llor C, Sierra N, Hernandez S, Morgas A, Hernandez M, Bayona C. The higher the number of daily doses of antibiotic treatment in lower respiratory tract infections the worse the compliance. *J Antimicrob Chemother* 2009;63:396-9.
 - [6] Kardas P. Patient compliance with antibiotic treatment for respiratory tract infections. *J Antimicrob Chemother* 2002;49:897-903.
 - [7] Litlekare I, Blix HS, Rønning M. Antibiotikaforbruk i Norge [Antibiotic use in Norway]. *Tidsskr Nor Laegeforen* 2008;128:2324-9 (English summary).
 - [8] NORM/NORM-VET 2009. Usage of antimicrobial agents and occurrence of antimicrobial resistance in Norway. Tromsø/Oslo 2010. ISSN 1502-2307 (print)/1890-9965 (electronic). Available at: <http://www.unn.no/summary-2010/category21917.html>
 - [9] Craig WA. Pharmacokinetic/pharmacodynamic parameters: Rationale for dosing of mice and men. *Clin Infect Dis* 1998;26:1-12.
 - [10] Høiby EA, Walstad RA. Vi bør bli bedre til å dosere antibiotika [We should improve our skills in antibiotic dosing]. *Tidsskr Nor Laegeforen* 2008;128:2750.
 - [11] Cals JW, Hopstaken RM, Le Doux PH, Driessen GA, Nelemans PJ, Dinana GJ. Dose timing and patient compliance with two antibiotic regimens for lower respiratory tract infection in primary care. *Int J Antimicrob Agents* 2008;31:531-6.
 - [12] Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005;353:487-97.
 - [13] Llor C, Hernandez S, Sierra N, Moragas A, Hernandez M, Bayona C. Association between use of rapid antigen detection tests and adherence to antibiotics in suspected streptococcal pharyngitis. *Scand J Prim Health Care* 2010;28:12-17.
 - [14] Grittih S. A review of the factors associated with patient compliance and the taking of prescribed medicines. *Br J Gen Pract* 1990;40:114-16.